IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

SEPRACOR INC., Plaintiff, vs. DEY, L.P. and DEY, INC., Defendants.	C.A. No. 06-113-JJF CONSOLIDATED
SEPRACOR INC., Plaintiff, vs. BARR LABORATORIES, INC. Defendant.	

DECLARATION OF IMRON T. ALY IN SUPPORT OF BARR'S REBUTTAL MEMORANDUM REGARDING CLAIM CONSTRUCTION

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Attorneys for Defendant Barr Laboratories, Inc.

I, IMRON T. ALY, declare and state that:

1. I am a partner at the law firm of Winston & Strawn LLP, located in Chicago, Illinois. I am counsel to Defendant Barr Laboratories, Inc. for this matter.

2. Attached hereto as Exhibit 22 is a true and correct copy of the Notice of Allowability for U.S. Patent 5,362,755 dated July 26, 1994.

3. Attached hereto as Exhibit 23 is a true and correct copy of the T. Scott Johnson Declaration dated May 11, 1994 and submitted to the U.S. Patent Office.

4. Attached hereto as Exhibit 24 is a true and correct copy of the following article: James W. Morton et al, *The Reversibility of Chronic Bronchitis, Asthma, and Emphysema*, Dis. Chest 53:126-132 (1968).

5. Attached hereto as Exhibit 25 is a true and correct copy of the following article: Alain Lurie et al, *Long Term Management of Reversible Obstructive Airway Disease in Adults*, Lung Suppl:154 (1990).

6. Attached hereto as Exhibit 26 is a true and correct copy of a letter from Imron T. Aly to Preston K. Ratliff II dated April 7, 2008.

7. Attached hereto as Exhibit 27 is a true and correct copy of a letter from Imron T. Aly to Preston K. Ratliff II dated April 30, 2008.

I declare under penalty of perjury under the laws of the state of Illinois that the foregoing is true and correct to the best of my knowledge and that this declaration was executed on this 1st day of May, 2008 at Chicago, Illinois.

By: _____
IMRON T. ALY

Exhibit 22

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
08/163,581	12/07/93	BARBERICH	SPC8905

EXAMINER: HENLEY III, R

ART UNIT: 1205 | PAPER NUMBER: 10

PHILIP E. HANSEN
HESLIN & ROTHENBERG, P.C.
5 COLUMBIA CIRCLE
ALBANY, NY 12203-5160

DATE MAILED: 07/26/94

NOTICE OF ALLOWABILITY

PART I.

1. ☒ This communication is responsive to The Amendment + declaration filed May 11, 1994
2. ☒ All the claims being allowable. PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice Of Allowance And Issue Fee Due or other appropriate communication will be sent in due course.
3. ☒ The allowed claims are 1-6 and 8 (renumbered as 1-7 respectively).
4. ☐ The drawings filed on _____ are acceptable.
5. ☐ Acknowledgment is made of the claim for priority under 35 U.S.C. 119. The certified copy has [_] been received. [_] not been received. [_] been filed in parent application Serial No. _____ filed on _____
6. ☒ Note the attached Examiner's Amendment.
7. ☒ Note the attached Examiner Interview Summary Record, PTOL-413.
8. ☒ Note the attached Examiner's Statement of Reasons for Allowance.
9. ☐ Note the attached NOTICE OF REFERENCES CITED, PTO-892.
10. ☐ Note the attached INFORMATION DISCLOSURE CITATION, PTO-1449.

PART II.

A SHORTENED STATUTORY PERIOD FOR RESPONSE to comply with the requirements noted below is set to EXPIRE THREE MONTHS FROM THE "DATE MAILED" indicated on this form. Failure to timely comply will result in the ABANDONMENT of this application. Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

1. ☐ Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL APPLICATION, PTO-152, which discloses that the oath or declaration is deficient. A SUBSTITUTE OATH OR DECLARATION IS REQUIRED.
2. ☐ APPLICANT MUST MAKE THE DRAWING CHANGES INDICATED BELOW IN THE MANNER SET FORTH ON THE REVERSE SIDE OF THIS PAPER.
   a. ☐ Drawing informalities are indicated on the NOTICE RE PATENT DRAWINGS, PTO-948, attached hereto or to Paper No. _____. CORRECTION IS REQUIRED.
   b. ☐ The proposed drawing correction filed on _____ has been approved by the examiner. CORRECTION IS REQUIRED.
   c. ☐ Approved drawing corrections are described by the examiner in the attached EXAMINER'S AMENDMENT. CORRECTION IS REQUIRED.
   d. ☐ Formal drawings are now REQUIRED.

Any response to this letter should include in the upper right hand corner, the following information from the NOTICE OF ALLOWANCE AND ISSUE FEE DUE: ISSUE BATCH NUMBER, DATE OF THE NOTICE OF ALLOWANCE, AND SERIAL NUMBER.

Attachments:

- ✓ Examiner's Amendment
- ✓ Examiner Interview Summary Record, PTOL-413
- ✓ Reasons for Allowance
- _ Notice of References Cited, PTO-892
- _ Information Disclosure Citation, PTO-1449
- _ Notice of Informal Application, PTO-152
- _ Notice re Patent Drawings, PTO-948
- _ Listing of Bonded Draftsmen
- _ Other

RAYMOND [illegible] HENLEY III
PRIMARY EXAMINER
GROUP 120 - ART UNIT 125

EXAMINER'S AMENDMENT/REASONS FOR ALLOWANCE

An Examiner's Amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 C.F.R. § 1.312. To ensure consideration of such an amendment, it **MUST** be submitted no later than the payment of the Issue Fee.

Authorization for this Examiner's Amendment was given in a telephone interview with Philip E. Hansen on July 13, 1994.

The application has been amended as follows:

IN THE CLAIMS:

In claims 1 and 6, line 4, ---chronically--- has been inserted before the word "administering".

In claim 6, line 3, ---chronic administration of racemic--- has been inserted before the word "albuterol"..

IN THE ABSTRACT:

At the last line, ---chronic administration of racemic--- has been inserted before the term "albuterol".

The following is an Examiner's Statement of Reasons for Allowance:

Applicants' amendment and the declaration of T. Scott Johnson filed May 11, 1994 have been received, entered and favorably considered. The Examiner agrees

with the statements made by both applicants and the declarant that support exists in the present specification for avoidance of the side effects associated with chronic therapy for asthma. Moreover, it is the Examiner's opinion that it would not have been expected from the prior art of record that the R(-) isomer of albuterol would possess the improved side effect profile as established in the declaration of Dr. Aberg filed July 23, 1993, i.e., that the R(-) isomer of albuterol does not cause the hypersensitivity reaction normally associated with long-term racemic albuterol administration in patients suffering from asthma. This fact is highly significant and compels the Examiner to conclude that the presently claimed invention would not have been obvious under 35 U.S.C. § 103. The Examiner is guided in his opinion by the finding of the Board of Patent Appeals and Interferences in the unpublished decision of Ex parte Ferrari et al. (Appeal No. 629-61) dated January 28, 1987 in which a similar factual situation existed. Further comments relating to this decision as well as the significance of the hypersensitivity reaction associated with racemic albuterol administration, which are hereby adopted by the Examiner, are presented in the paper entitled "Record of Telephonic Interview" filed by applicants on August 5, 1993.

Thus, for the reasons above, claims 1-6 and 8 are deemed to be allowable.

Any comments considered necessary by applicant must be submitted no later than the payment of the Issue Fee and, to avoid processing delays, should preferably **accompany** the Issue Fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

RAYMOND J. HENLEY III
PATENT EXAMINER
GROUP 120 - ART UNIT 125

Exhibit 23

Part #38

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Timothy J. Barberich and James W. Young

Applicant's Docket No.: SPC89-05 Group Art Unit: 1205

Filed: December 7, 1993 Examiner: R. Henley III

Title: METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(-) ALBUTEROL

DECLARATION UNDER 37 C.F.R. §1.132

To: Hon. Commissioner of Patents and Trademarks
Washington, D.C. 20231

Dear Sir:

I, T. Scott Johnson, declare:

1. I reside at 415 Nashwatuc Road, Concord, Massachusetts.

2. I earned a Bachelor of Science degree from the University of Alabama in 1969 and an M.D. degree from the University of Alabama School of Medicine in 1973. I am certified by the American Board of Internal Medicine with a subspecialty in Pulmonary Disease. I have been a Clinical and Research Fellow in Pulmonary Disease at the University of Colorado Medical Center, and, until 1991 I was Assistant Professor of Medicine at Harvard Medical School, where I was an Attending Consultant in Pulmonary Disease.

3. I am the author of 16 original articles, 8 review articles and a textbook on subjects relating to pulmonary disease.

4. I am presently a Managing Partner of Medical Portfolio Management, Inc., in Cambridge, Massachusetts. In this capacity, I have been retained by Sepracor, Inc.

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(assignee of the above-identified application) as a paid consultant on an hourly basis. My compensation from Sepracor is unaffected by any change in status of the above-identified application, and I will not benefit financially from issuance of a patent thereon.

5. I have reviewed and do understand the contents of the above-identified application, which is directed to a method for treating asthma while avoiding the side effects associated with racemic albuterol by using the pure R-enantiomer of albuterol. As a result of my knowledge and experience I make the following observation:

The term "chronic" does not appear in the specification. However, the concept of chronic administration is implicit in the description of modes of administration that is found in the specification. In particular, on page 4 in the paragraph extending from line 4 to line 13, the concepts of the two modes of therapy (acute and chronic) are discussed. In the first mode (acute) the albuterol is administered "after onset of asthma". In the second, albuterol is administered "prophylactically, that is, before the bronchiospasm [sic] begins in an asthma attack, to prevent its occurrence.."

Asthma is defined (Webster's Medical Desk Dictionary, 1986 edition) as "a condition often of allergic origin that is marked by continuous or paroxysmal labored breathing accompanied by wheezing, by a sense of constriction in the chest, and often by attacks of coughing or gasping". To be noted is the distinction between asthma (a condition or disease state) and an asthmatic attack (an acute episode of coughing, wheezing or gasping), which often accompanies the general disease state. Asthmatic attacks can be treated acutely; asthma is treated chronically.

Albuterol is, in the presently claimed invention, intended to be administered to "an individual who has asthma" (line 5 to 6). Since the patient has asthma (i.e suffers from a disease state), and treatment is to be prophylactic, treatment would have to be chronic. If the treatment were not chronic, cessation of administration might or might not lead to an immediate attack, but it would certainly lead to

reestablishment of the disease condition.

Thus, although the term "chronic" is not used, its implication is clear in the description of prophylactic therapy. Indeed, since one is commonly not able to predict the onset of an acute attack, and since current practice in the treatment of asthma favors the treatment of the underlying disease state, many patients are treated chronically. Thus the person of skill in the art would understand that the application was referring to chronic therapy when it speaks of either prophylactic or periodic administration.

That the concept of chronic medication is envisioned is further supported by the disclosure on page 5, line 6 to line 9, regarding oral therapy. An oral regimen of "1 to about 8 mg two to four times daily" would not make sense as acute therapy.

6. I further declare that all statements of the foregoing declaration made of my own knowledge are true and that all statements made upon information and belief are believed true and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the above identified application or any patent issuing thereon.

Signed by me this 11th day of May, 1994.

T Scott Johnson

T. Scott Johnson

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May 11, 1994

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MAY 12 1994

Exhibit 24

The Reversibility of Chronic Bronchitis, Asthma and Emphysema*

JAMES W. MORTON, M.D. AND KENNETH W. TURNBULL, B.A.
Vancouver, B. C., Canada

PRIOR TO THE PUBLICATION OF THE *Ciba Guest Symposium* in 1959,[1] the terms chronic bronchitis, asthma and emphysema were used very loosely. Chronic bronchitis was considered by some[2] to be a symptom rather than a disease entity. Asthma was a generic term; Dorland's *Medical Dictionary* lists some 42 types, including such widely varying conditions as bronchial, cardiac, renal and sexual asthma. The common factor was "wheezing." Emphysema was a condition defined in various terms depending on whether one was a clinician, radiologist, physiologist or a pathologist. The common factor was presumably overinflation, the Greek derivation of the word referring to the gross anatomic picture of the lung. The *Ciba Guest Symposium* did a great deal to clarify this confusion, both directly and indirectly. Its definition of chronic bronchitis is clear, concise and widely used. Its definitions of asthma and emphysema, though open to criticism, stimulated others to attempt improvements.

Chronic bronchitis was not classified as an obstructive lung disease by this group of 17 prominent British scientists, nor in terms of its reversibility, as were the other two conditions in question. Since 1959, Bates *et al*[3] have shown that though some chronic bronchitics have completely normal lung function, many demonstrate the presence of bronchial obstruction. Some of the cases of Fletcher *et al*[4] of chronic bronchitis had as severe a degree of obstruction as their emphysematous subjects. For this reason, chronic bronchitis may be classified along with asthma and emphysema as an obstructive lung disease.

The *Ciba Guest Symposium* recognized the fact that the term emphysema indicated a morbid anatomic state, and since no good correlation existed between the pathology of this disease on the one hand and the clinical, radiologic and physiologic data on the other, they avoided the use of the term. It was replaced by "irreversible obstructive lung disease," to differentiate it from "reversible obstructive lung disease" or asthma. Their definitions, then, are based on reversibility and are stated as follows:

Intermittent or reversible obstructive lung disease: asthma. This refers to the condition of subjects with widespread narrowing of the bronchial airways, which changes its severity over short periods of time either spontaneously or under treatment, and is not due to cardiovascular disease. The clinical characteristics are abnormal breathlessness, which may be paroxysmal or persistent, wheezing, and in most cases relief by bronchodilator drugs (including corticosteroids).

"Irreversible or persistent obstructive lung disease" refers to widespread narrowing of the bronchial airways, which has been present for more than one year and which is unaffected by bronchodilator drugs (including corticosteroids).

These are essentially therapeutic definitions. There is a tendency, however, to use them diagnostically; indeed the Ciba group equate reversible obstructive lung disease with asthma. Observation of a large number of patients passing through this lung function laboratory suggested that though most asthmatics respond completely or partially to a bronchodilator, some do not respond at all, and though most emphysematous patients do not respond at all to a bronchodilator, some respond at least

*From the Respiratory Function Laboratory, Department of Medicine, University of British Columbia.

Supported by a grant from the Tuberculous and Disabled Veterans' Association.

partially. The latter statement also appeared to apply to chronic bronchitics.

The first purpose of this paper then, is to study the response to a bronchodilator drug of a series of patients suffering from chronic bronchitis, asthma, emphysema or a combination of these, in an attempt to clarify the validity of definitions based on reversibility.

A portion of the patients who had either asthma alone or asthma and chronic bronchitis combined were on corticosteroid therapy at the time of study. They appeared to respond to the bronchodilator as well as those who were not on corticosteroid therapy.

The second purpose of this paper is to study the reversibility of this group of patients and to discuss the reasons for this apparent response.

Material and Methods

The charts of every patient seen in the lung function laboratory over an 18-month period were reviewed. To qualify for the study, each patient had to have a satisfactory history recorded in the laboratory, a maximal breathing capacity (MBC) less than 80 per cent of the predicted value, an MBC performed after a bronchodilator and a steady state diffusing capacity. A patient with an MBC greater than 80 per cent of the predicted value was disqualified, since this is within the range of normal and therefore could not be expected to improve after a bronchodilator. They were then divided into groups according to whether they had chronic bronchitis, asthma, emphysema, or a combination of these. A final group consisted of a miscellaneous series of cases including pulmonary fibrosis of various types and cardiovascular disease. The definitions used were as follows:

1. Chronic bronchitis: Chronic cough with phlegm for most days for at least three months for at least two successive years. This is a clinical definition, essentially that used by the Ciba Guest Symposium.
2. Asthma: Periodic attacks of wheezing and shortness of breath, with relatively normal periods between, excluding cardiovascular disease. This is a clinical definition, essentially that used by Bates and Christie[5] and by Baum.[6]
3. Emphysema: Obstructive lung disease as measured by the MBC, and a low steady state diffusing capacity. This is a physiologic definition based on the pathologic definition of the World Health Organization[7] which states: "Emphysema is a condition of the lung characterized by increase beyond the normal in the size of the air spaces distal to the terminal bronchiole, with destructive changes in their walls." There is indirect evidence to conclude that this is a satisfactory physiologic definition of emphysema.[8,9]

The patients could be classified into five groups, as follows: 1) asthma alone; 2) asthma and chronic bronchitis; 3) chronic bronchitis alone; 4) chronic bronchitis and emphysema. Group 5 consisted of a miscellaneous series of chest diseases, none of which had any of the three conditions to be investigated. There were two cases of emphysema alone, asthma, chronic bronchitis and emphysema combined and asthma and emphysema combined. Because of their small numbers, these were not included in the study. The fact that there was not a sufficient number of "dry" emphysemas is unfortunate. Any response obtained from the Group 4 patients with chronic bronchitis and emphysema might be said to be due to the chronic bronchitis alone.

Diffusing capacity was measured by a modification of the steady state method of Bates, Boucot and Dormer.[10] A value less than 80 per cent of that predicted by the regression equation of Bates and associates[3] was considered abnormal. The MBC was performed over a 15 second period using a low resistance valve and a 350 L Tissot spirometer. This was repeated 15 minutes after the administration of 2 ml of a 1/200 dilution of isoproterenol delivered by an oxygen-generated nebulizer. Results were expressed as a percentage of the predicted value based on the regression equation of Baldwin *et al.*[11] Standard statistical techniques were used to determine the mean age, the mean changes in MBC, and the standard deviations of the samples.[12] The statistical significance of the means of each group was then determined using the student "t" test. The level of a significant result was set at $p=0.05$ and of a highly significant result at $p=0.01$.

Volume 54, No. 2
February, 1968

TABLE 1—NUMBER, AGE AND SEX DISTRIBUTION BY GROUP

Group	No.	Age		Sex	
		Mean Age Years	Range Years	Men	Women
I	43	51.5	15-79	28	15
II	24	58.5	32-75	19	5
III	39	57.7	31-80	34	5
IV	39	59.8	32-81	33	6
V	27	53.5	32-77	19	8

RESULTS AND DISCUSSION

Table 1 shows the number in each group, the mean age, age range and sex distribution. Except for Groups 2 and 5 the numbers are similar. The mean ages are also comparable, that of the asthmatic group of patients being slightly lower. The age range in this group has a wider variation as might be expected. The sex distribution is predominantly men in all groups. The mean improvement in MBC after isoproterenol, expressed as the difference in the percentage of the predicted values, is shown in Table 2, along with their standard deviations and levels of significance (i.e. increase in MBC = per cent of predicted value before less per cent of predicted value after bronchodilator). The men improvement in the asthmatic group was 19.8. As might be expected, those patients of Group 2 who had both asthma and chronic bronchitis responded to a lesser degree (15.3 per cent), but the difference was not statistically significant when compared with Group 1. The mean improvement in the chronic bronchitics (Group 3) was 6.1 per cent, a highly significant difference when compared with asthma alone. Groups 4 (emphysema and chronic bronchitis) and five (miscellaneous) showed a similar increase in MBC (5.1 per cent and 7.3 per cent respectively), and these differences were also found to be highly significant when compared with asthmatic subjects of Group 1.

TABLE 2—INCREASE IN MBC AFTER ISOPROTERENOL BY GROUP

Group	Increase in MBC Per Cent Predicted Normal		Level of Significance* P
	Mean	5.0	
I	19.8	±16.3	—
II	15.3	±10.5	0.20
III	6.1	± 8.7	0.01
IV	5.1	± 7.0	0.01
V	7.3	±13.7	0.01

*Compared with Group 1.

It would appear, then, that on the average, asthma, whether occurring alone or with chronic bronchitis, responds well to the bronchodilator while chronic bronchitis occurring alone or combined with emphysema responds to a much smaller degree. The terms "reversible" and "irreversible" however, are misleading. "Reversible" does not indicate complete reversibility. Table 3 shows the improvement in MBC arranged in intervals for each group, together with the percentage of patients whose MBC rose to greather than 80 per cent of the predicted value. Only 33 per cent of Group 1 and 29 per cent of Group 2 were completely reversible in the sense that their MBC rose above the 80 per cent level. Furthermore, "irreversible" does not indicate complete irreversibility since only 51.0 per cent of Group 3 and 57 per cent of Group 4 improved their MBC less than 5 per cent after the bronchodilator. The relatively poor response of some Group 1 and 2 patients and the relatively good response of some Group 3 and 4 patients is also shown in Table 3. This is illustrated graphically in Figure 1, in which the distribution curves of the responses of our five groups are drawn. From the figure it can be seen that the spread of the asthmatic patients is the greatest and

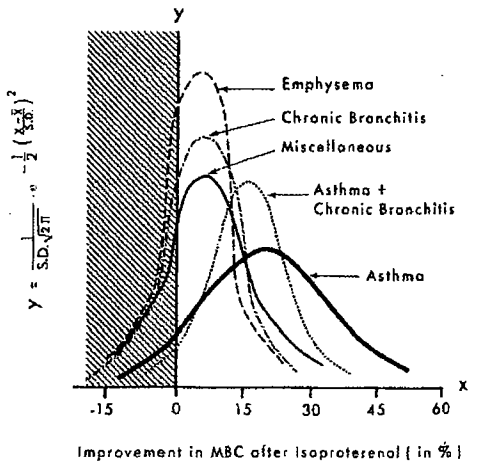

FIGURE 1

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TABLE 3—IMPROVE
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Group	0-4 Per Cent
I	21
II	21
III	51
IV	57
V	37

that all other groups are partially enclosed by the distribution curves of each other.

One could conclude, then, that though on the average asthma responds significantly better to a bronchodilator than does chronic bronchitis alone or combined with emphysema, this is of little aid in the diagnosis of the individual case since there is so much overlapping in the degree of reversibility. Some asthmatics respond relatively poorly, while some chronic bronchitics alone or combined with emphysema respond relatively well. It is of some interest to consider why this is so.

Perhaps firstly one must decide whether or not the diagnoses on the patients presented here are correct. Asthma, chronic bronchitis and emphysema are very similar conditions in that physiologically they all demonstrate varying degrees of obstruction and varying degrees of overinflation. Many of the clinical and radiologic signs are based on these two physiologic abnormalities. Accordingly, any study involving these three conditions may be criticized on the grounds that their definitions are incorrect. Although it is realized these are not perfect, it is felt that they are, at the present, the best available. This is especially so of the diagnosis of emphysema in which either modern radiologic techniques[8] or physiologic tests,[3,9] are believed to be necessary.

The cause or causes of bronchial obstruction in asthma, chronic bronchitis and emphysema are difficult to state with any authority. In asthma there is said to be smooth muscle contraction, edema of the bronchial mucosa and excessive bronchial secretions. A reasonable explanation for the cause of obstruction in chronic bronchitis is that pathologically it has been shown that there is a hypertrophy of mucous glands[13] and by definition there are excessive mucous secretions. The cause of obstruction in emphysema is more obscure. In most, chronic bronchitis is present. It is said that loose strands of ruptured alveoli may result in a ball valve mechanism, the strand obstructing the bronchiole on expiration. A third possibility is that in a combination of obstruction in the smaller air passages and a loss of elastic tissue, the alveoli balloon out on expiration and collapse the bronchiole. Since the latter two are purely mechanical, it would seem unlikely that a bronchodilator would have any effect on them. One would expect it to act either on the contracted smooth muscle, edema of the bronchiole mucosa or the excessive bronchial secretions.

It is well known that isoproterenol acts on beta adrenergic receptors.[14-16] Such receptors are found in the heart, smooth muscles of the bronchi, skeletal vasculature and alimentary tract. The drug relaxes smooth muscle when the tone is high, an action most pronounced in the bronchi and gastrointestinal tract. There is no evidence in the literature to suggest isoproterenol reduces edema, though this does not mean such an action does not exist. There is also no suggestion that isoproterenol is an expectorant. It is well known, however, that inhalation of any substance may stimulate cough with expectoration of bronchial secretions. Casual observation in our patients did not suggest this played a significant role in the relief of obstruction. Furthermore, Zohman and Williams[17] have shown that cough induced by placebo did not improve the degree of obstruction and they conclude that isoproterenol has a bronchodilator effect which

TABLE 3—IMPROVEMENT IN MBC BY INTERVALS: (PERCENTAGE OF PATIENTS IN EACH GROUP)

Group	0-4 Per Cent	5-10 Per Cent	10 Per Cent	To 80 Per Cent
I	21	5	74	33
II	21	17	62	29
III	51	23	26	10
IV	57	23	20	0
V	37	26	37	22

TABLE 4—RESPONSE TO ISOPROTERENOL OF 12 ASTHMATIC PATIENTS RECEIVING CORTICOSTEROIDS

No.	Age	Yrs.	Sex M	Sex W	Additional Chronic Bronchitis	Increase in MBC Per Cent Predicted Normal Mean	Increase in MBC Per Cent Predicted Normal S.D.
12	50	21-68	7	5	8	21.8	±7.9

is independent of the raising of secretions. This suggests that the drug acts only to relieve bronchospasm. If this is so, the good response of asthma is satisfactorily explained, but one must assume that at least a minor degree of bronchospasm is present also in chronic bronchitis alone or combined with emphysema. A similar assumption must also be made to explain the improvement in our group of miscellaneous cases.

There is one other possibility which might explain the improvement of the MBC after the administration of isoproterenol. Lewis and Morton[18] showed that the MBC in normal subjects improved significantly after the injection of epinephrine. They pointed out the fact that adrenalin is said to improve muscular efficiency by increasing the blood supply to the muscles, preferentially to the thoracic muscles, and they suggested this might be the cause of the improvement in the MBC after epinephrine, in normal subjects.

It has also been shown that isoproterenol increases the flow of blood to skeletal muscle, probably as the result of vasodilation.[16] This would satisfactorily explain the improvement in MBC in chronic bronchitis, chronic bronchitis and emphysema and in the miscellaneous group. It might not explain the improvement in the asthmatic patients, since Cookson and Reed[19] showed such subjects responded significantly less intensely than their controls to the vasodilating effects of isoproterenol. Asthmatics, according to these authors, are believed to exhibit a partial blockade of the smooth muscle beta receptors to adrenergic stimulation. If the possible indirect action of isoproterenol is accepted, one must assume the aerosol drug is absorbed and circulated. This would appear to occur since the side effects suggest this.[20]

The wide variation in the degree of response to a bronchodilator from patient to patient seen in Table 3 and Figure 1 might be explained in three ways. The first of these is that the aerosol drug may not have reached the obstructed bronchiole in some cases. If this is so, one might expect to find that patients with the most obstructed bronchi have the least response. Scattergrams in which the observed MBC is plotted against the percentage of improvement in our five groups did not suggest this. Other possibilities are that increased secretions may prevent the drug from coming into intimate contact with the bronchial mucosa or that a type of "fastness" might be present.

One may conclude, then, that bronchospasm is the main cause of bronchial obstruction in asthma. In chronic bronchitis alone or combined with emphysema, or in the miscellaneous groups, bronchospasm may also occur. In all conditions discussed, the bronchodilator drug may act directly on smooth muscle or indirectly by improving the blood supply of skeletal muscle, although in asthma the latter appears less likely. The varying response in all conditions may depend on a varying degree of bronchospasm, the varying amounts absorbed resulting in a varying indirect action, the degree of fastness to the drug and the fact that the bronchodilator may not reach bronchial smooth muscle due to the presence of secretions.

Of further interest in regard to the reversibility of asthma is the response to isoproterenol of patients on corticosteroid therapy. Twelve of our asthmatic subjects fell into this category. The results are shown in Table 4. Their mean age was 50 years with a range of 21 to 68 years; there were seven men and five women. Eight of the 12 had an additional diagnosis of chronic bronchitis. The mean improvement in MBC after isoproterenol was 21.8 per cent (S.D. ∓7.9 per cent). This compares favorably with the mean improvement of 19.8 per cent found in the asthmatics of Group 1 and 15.3 per cent improvement in Group 2 patients with combined asthma and chronic bronchitis. Similar results have been reported by other authors.[21-22]

The action of corticosteroids on the bronchial mucosa has been studied by Collins, Cordell and Pearson[24] who showed by bron-

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chial biopsy that the eosinophilic infiltration, thickening of the bronchial mucosa and chronic inflammation reverted to normal after steroid therapy. Keeney and Palmer[25] compared their asthmatics who were treated with steroids with a similar group of asthmatics not treated with this drug. They felt the pathologic improvement in the treated subjects was related to the duration of the steroid therapy and concluded that "the corticosteroids, by antagonizing the inflammatory reaction of the bronchial and bronchiolar walls, diminish mucous gland activity, reduce edema and congestion and lastly decrease epithelial desquamation." Goodman and Gillman[14] confirm the fact that steroids inhibit the inflammatory response whether the responsible agent is mechanical, chemical or immunologic.

One can probably conclude that in asthma alone or combined with chronic bronchitis, the steroids act only on the inflammatory components of bronchial obstruction and that isoproterenol further improves the degree of obstruction by acting on the beta-adrenergic receptors, relieving the increased bronchial smooth muscle tone.

Summary

1. The response to a bronchodilator of a series of patients with asthma, chronic bronchitis, emphysema, or a combination of these has been studied and compared with a group of patients suffering from other miscellaneous conditions.

2. Although the mean improvement after a bronchodilator in patients with asthma alone or combined with chronic bronchitis is significantly better than the improvement in chronic bronchitis alone or combined with emphysema, the degree of overlap is so great that a diagnosis based on reversibility is of little use in the individual case.

3. The additive effects of a bronchodilator and corticosteroids in asthma alone or combined with chronic bronchitis have been demonstrated.

Resumen

1. Se contrastan los resultados obtenidos con un agente broncodilatador en pacientes con asma, bronquitis crónica, enfisema o una combinación de estas afecciones, con los observados en otros sujetos afectos de trastornos diversos.

2. Si bien la mejoría obtenida con el broncodilatador en pacientes con asma simple o combinada con bronquitis crónica es superior al observado en aquellos con solo bronquitis crónica o combinada con enfisema, esta diferencia carece de valor como criterio diagnóstico en casos individuales.

3. El efecto aditivo de un broncodilatador y los corticoesteroides en el asma simple o combinada con bronquitis crónica ha sido comprobado.

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The Department of Otolaryngology, Illinois Eye and Ear Infirmary and the College of Medicine, University of Illinois at the Medical Center, will conduct a postgraduate course in Laryngology and Bronchoesophagology from March 25 through April 6, 1968. This course is limited to 15 physicians and will be under the direction of Paul H. Holinger, M.D. It will be held largely at the new Illinois Eye and Ear Infirmary, 1855 West Taylor Street, Chicago, and will include visits to a number of Chicago hospitals. Instruction will be provided by means of animal demonstrations and practice in bronchoscopy and esophagoscopy, diagnostic and surgical clinics, as well as didactic lectures.

Interested registrants should write directly to the Department of Otolaryngology, College of Medicine, University of Illinois at the Medical Center, P. O. Box 6998, Chicago, Illinois 60680.

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Lung (1990) Suppl:154–167

Lung

Long-term Management of Reversible Obstructive Airways Disease in Adults

Alain Lurie,[1,2] Fotis D. Vlastos,[2] Daniel J. Dusser,[2] Georges Strauch,[1] and Jean Marsac[2]

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Abstract. The goals of the long-term management of reversible obstructive airways disease (ROAD) are to find the minimum treatment that controls symptoms, allows resumption of normal life, prevents severe attack and death, and controls airflow obstruction. ROADs include asthma, chronic bronchitis, and emphysema. Although the differential diagnosis between these different entities may be difficult, they share the same possibilities of pharmacotherapy, including bronchodilator and antiinflammatory drugs. β_2-agonists administered via inhaled route produce the best bronchodilator/side effects ratio, provided that the drugs reach the bronchi. This underlines the importance of a proper inhalation technique when using a metered-dose inhaler. In patients with hand-breath coordination problems, powder inhalers or spacer devices are useful to ameliorate the therapeutic efficacy of inhaled drugs. Anticholinergic agents are usually less potent bronchodilators than inhaled β_2 agonists in asthma, but they may have additive effects when associated with β_2 agonists. Only a therapeutic trial with peak-flow monitoring can demonstrate the efficacy of anticholinergic drugs in individuals. Theophylline's kinetics are characterized by a narrow therapeutic index with high inter- and intraindividual variabilities. Sodium cromoglycate and nedocromil sodium are antiallergic drugs, the efficacy of which has been demonstrated in controlled studies. Corticosteroids are the most efficient antiasthma drugs. Inhaled corticosteroid dosing should be tailored to each individual. If inhaled corticosteroid therapy is used in an oral corticosparing attempt, patients should be followed-up during several months. The management of ROAD includes the diagnostic procedures, the identification of triggers and inducers of airways obstruction, the assessment of severity of the disease, and then the treatment and education of the patient. Strategy design to achieve proper use of drugs by patients is discussed.

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Key words: Bronchial obstruction—Asthma—Reversible obstructive airways disease—Aerosols—Treatment.

Introduction

Reversible obstructive airways disease (ROAD) include asthma, chronic bronchitis, and emphysema. The diagnosis of asthma rests upon anamnestic arguments. If the clinical features are not typical of asthma, the diagnosis may be helped by looking for diurnal variation of peak expiratory flow values or, according to the results of baseline pulmonary test functions, by measuring response to either nonspecific stimuli such as histamine and methacholine, or to an inhaled β_2-agonist. Clear-cut differentiation between chronic bronchitis, emphysema, and asthma is sometimes impossible. Some patients with chronic bronchitis or emphysema present important bronchial reversibility [1]. In contrast, some patients with asthma present little bronchial reversibility in acute trials and their bronchial obstruction may tend to diminish with time [2]. Comparing the pulmonary function tests before and after an acute bronchodilator administration is of limited value if one wants to separate chronic obstructive lung disease from asthma. Furthermore, some patients who appear at first to be relatively unresponsive to β_2-agonists may respond later to repeated bronchodilator challenges [3]. A trial with corticosteroids may be required to insure that reversibility has not been underdiagnosed [4]. If the trial does not show any improvement of bronchial obstruction, corticosteroids may be stopped within 3 days [4]. In contrast, when bronchodilation is observed, inhaled corticosteroids are indicated. If a trial with inhaled corticosteroids is decided, high dosages should be used, because they have been shown to produce better therapeutic effects [5]. The patients with bronchial response to corticosteroids are then mostly managed in a similar way to patients with asthma [6].

One must write or talk with modesty about the management of asthma because although the modern pharmacotherapy of the disease may be highly efficient, more patients die of bronchial asthma than previously. The increasing mortality in patients with asthma during the last three decades did not receive clear explanations [7, 8]. Each hypothesis aiming to elucidate this increased mortality may appear unlikely or insufficient to explain all the available data. These hypothesis belong either to the epidemiology (change in classification of asthma in 1979, increased prevalence and more virulence of asthma, shift in the age distribution of incidence), or to the management of the disease (inadequate assessment and treatment, iatrogenicity) [8].

Pathophysiologic Features of ROADs and Their Therapeutic Implications

Bronchial inflammation and bronchial smooth muscle spasm are the two main pathophysiologic components of asthma [9]. Release of spasmogenic and/or inflammatory mediators from cells in the airways produces and maintains the bronchial pathologic alterations observed in asthma. These cellular mecha-

nisms are better understood in allergic asthma, where the mediators released after the allergenic contact have been shown to recruit inflammatory cells. In turn, these cells release other mediators with inflammatory and spasmogenic actions [9]. Bronchial inflammation has been shown to play an important role in the mechanisms underlying bronchial hyperreactivity, bronchial obstruction, and the symptoms of asthma. ROADs other than asthma may also implicate bronchial smooth muscle spasm and bronchial inflammation associated with irreversible forms of airway obstruction such as loss of bronchial elastic recoil and fibrotic distortion. The pharmacotherapy of ROAD results from these pathophysiologic features. Treatments include bronchodilator and anti-inflammatory drugs.

Pharmacotherapy of ROAD

Bronchodilator Drugs

The therapeutic efficacy of bronchodilators depends upon their dose. Increasing the dose of a bronchodilator may increase also its adverse effects. These adverse effects have been incriminated in the increase in mortality of asthma [8].

β_2 agonists. β_2 agonists are available for inhaled, oral, and parenteral administration. The oral route produces a more delayed onset of action than inhaled or parental route [10]. Oral and parenteral routes produce more pronounced side effects than the inhalation route [11]. Furthermore, the inhaled dose is much lower than that required when the drug is prescribed per os [12]. Therefore, inhalation of β-adrenergic agents produces the greatest benefits/side-effects ratio and is to be preferred for the treatment of ROAD. The importance of a good inhalation technique is discussed further on. Uncontrolled self-treatment with inhaled β_2-agonists may lead to excessive and unsupervised abuse that may delay hospital admission and anti-inflammatory treatment or that may even induce fatal cardiotoxicity [13]. Increase in deaths from asthma in New Zealand has been hypothesized to be due to overuse of high dose of β_2-agonists with home nebulizers and a subsequent underuse of an appropriate anti-inflammatory treatment [14].

The presently available inhaled β_2-agonists produce rapid bronchodilation, which reaches its maximum effect at about 15 min after inhalation and lasts for up to 6 h. They are prescribed at a dose of one to two puffs every 4–6 h. Two puffs should be taken 1 min apart. Patients should be instructed not to exceed 10–12 puffs daily. If a higher daily dose is required, therapeutic adjustment is preferable than to merely increase the daily number of puffs of β_2-agonists. The use of β-adrenergic agonists should not delay the use of corticosteroids, even if rapid relief from symptoms is obtained that diminishes the awareness of the patients about their disease [13].

Slow-release theophyllines. The bronchodilator effect of theophylline is directly related to the serum concentration of the drug. The optimal and safe effects of theophylline are observed at serum concentrations ranging from 7 to 15 μg/ml. Theophylline toxicity is well documented above the "safe" levels of serum concentrations of the drug. Side effects occur frequently following a loading dose and are avoidable when the treatment is started with low doses [15]. However, side effects may appear even within the subtherapeutic serum theophylline concentration range. The combination of slow-release theophylline with β-adrenergic agonists may produce additive therapeutic effects but is susceptible to more pronounced side effects [16]. Difficulties in the management of theophylline treatment are increased by factors that influence theophylline pharmacokinetics such as smoking, age, food, and drugs. The great intra- and intersubject variability in theophylline pharmacokinetics shows the importance of checking serum theophylline concentration in each individual.

Anticholinergic agents. Ipratropium bromide (Atrovent) and oxytropium bromide (Tersigat, Oxivent) are synthetic quaternary ammonium, chemically close to atropine. At present, no major side effects other than bitter taste have been reported for inhaled ipratropium, even if administered at very high doses. In stable asthma, the degree of bronchodilatation obtained with anticholinergic drugs is less than that obtained with β_2-agonists [17]. However, some patients with ROAD respond better to anticholinergic drugs than to β_2-agonists [18]. Factors that favor the good response to ipratropium bromide are nonallergic asthma, old age with long duration of asthma history, and mild bronchial obstruction [19]. The only way to identify a good responder is to perform a trial with the anticholinergic drug [20]. The optimal bronchodilatation following administration of ipratropium bromide is achieved after inhalation of 80 μg [17]. However, doses of 160 μg of ipratropium have been reported to reduce significantly the morning fall in peak expiratory flow rate of patients with asthma [21]. Following an inhaled dose of ipratropium, maximal bronchodilatation is observed in about 1–2 h. In chronic asthma, ipratropium bromide is prescribed at doses of two to three puffs every 4–6 h. Combined treatment with ipratropium bromide and β_2-agonists or theophylline has generally an enhanced or more prolonged effect than each treatment alone [22]. A pressurized aerosol containing both fenoterol and ipratropium bromide is currently available.

Nonbronchodilator Drugs

Nedocromil sodium and sodium cromoglycate. Sodium cromoglycate and nedocromil sodium share the same antiallergic properties [23]. They both inhibit the immediate bronchoconstriction induced by stimuli such as exercise, or inhalation of antigen, sulfur dioxide, or cold air [24, 25]. These agents can also attenuate the late asthmatic reactions in patients with allergic asthma [24]. In adult patients with chronic asthma, treatment with inhaled sodium cromoglycate resulted in significant improvement in asthmatic symptoms and peak ex-

piratory flow rates, as well as reduction in concomitant medications when compared to a placebo group [26]. Nedocromil sodium was shown to improve significantly asthmatic symptoms and lung functions in a placebo-controlled trial of 12 weeks in patients maintained on bronchodilators [27]. Nedocromil sodium has been shown to be effective in the treatment of ROAD, but its place in the strategy of treatment of asthma remains to be determined. Presently, sodium cromoglycate is considered as a first-line prophylactic treatment of asthma.

Corticosteroids. Corticosteroids constitute the most efficient anti-inflammatory drugs. Inhaled corticosteroids produce far less side effects than oral corticosteroids [28]. Inhaled doses up to 1000 μg/day of beclomethasone dipropionate may be used with minimal risks of side effects such as oral candidiasis and dysphonia. These local side effects may be minimized by rinsing the mouth and throat after each inhalation and by using a spacer device [29]. Systemic side effects of inhaled corticosteroids are infrequent up to a daily dose of 1500–2000 μg/day. At doses up to 1500 μg/day, 91% of patients treated with inhaled corticosteroids were shown to have both normal values of morning cortisol and normal response to adrenocorticotropic hormone [30]. Controlled clinical trials in asthmatic patients have demonstrated the therapeutic efficacy of all the presently available inhaled corticosteroids, namely, beclomethasone dipropionate, flunisolide, budesonide, and triamcinolone [31]. A relationship between dose and efficacy of inhaled corticosteroids has been reported. Treatment with inhaled corticosteroids may allow to decrease oral corticosteroids. The success rate of patients weaned off oral prednisone after a long-term administration of inhaled corticosteroids has been estimated by Toogood et al. using data from published studies [32]; the success rate has been found to reach 100% in studies of 4 months or less, while the averaged rate over a period of 24 months of follow-up was about 30%. Oral corticosteroids should be withdrawn with caution because fatal relapse of asthma may occur [33]; this indicates the importance to follow-up the weaning period with peak expiratory flow monitoring. The dosing regimen of inhaled corticosteroids has been a matter of controversy, probably due to differences in the groups studied: 2–4 times per day have been proposed [34]. Patients who present severe exacerbations of asthma during treatment with inhaled corticosteroids require oral or parenteral corticosteroids.

Other agents. So far, calcium channel blockers and α-adrenoceptor blockers have no defined role in the management of ROAD. The results of administration of prostaglandin E_1 or of several inflammatory mediators antagonists have not demonstrated any clinical efficacy [35]. Immunosuppressive agents such as methotrexate and azathioprine have currently no place in the management of ROAD. Antihistamines may be indicated for diseases associated with asthma such as allergic rhinitis. The data available for potassium channel activators may to consider these agents as potentially useful in the bronchodilator treatment [36]. Inhaled furosemide was shown to reduce allergen-induced asthma

but its place in the treatment of asthma requires further study [37]. In this paper, we will concentrate upon the three classes of bronchodilator drugs and the corticosteroid use in the care of patients with ROAD.

Management of ROAD

The management of ROAD associates the diagnostic procedures, already discussed in this paper, the identification of triggers and inducers of bronchial obstruction and the assessment of severity of the disease which is used to define a strategy of treatment and finally the education of the patient [38].

The Assessment of ROAD

Identification of inducers and triggers. The assessment of patients with ROAD include the investigation of all the pathologic conditions that may influence the course of the bronchial disease and that may be accessible to treatment. Agents that provoke acute exacerbation of asthma are usually referred as "triggers" while those that increase airway responsiveness to other stimuli are called "inducers" of asthma [39]. The first step of anti-inflammatory treatment to be considered is the treatment of triggers and inducers of asthma.

The role of allergy to environmental allergens in patients with asthma remains controversial [40, 41]. However, the prevalence of asthma has been shown to be lower in higher altitude, where the prevalence of positive skin tests to house dust mites is also lower than at the sea level [42]. Increased nonspecific bronchial hyperreactivity or allergen-specific bronchial reactivity has been demonstrated during pollen season in sensitive patients with asthma [43, 44]. Allergic symptoms and numbers of positive-prick skin tests were reported to increase with increasing severity of asthma in children [45]. Besides bronchial allergy, allergic rhinitis and sinusitis are often encountered. The cause-effect relationship between upper airways inflammation and induction of asthma is difficult to establish. Some investigators consider that both sinusitis and asthma are manifestations of the same underlying disease [46]. Others suggest that sinusitis can trigger and may aggravate ROAD [45, 47, 48]. Although few data exist that prove that sinusitis may cause or worsen asthma, it is a usual rule to look for and to treat an associated sinusitis in case of difficult-to-control ROAD.

Respiratory infections often aggravate asthma [49]. Viral infections are very frequent precipitating factors in children and adults with asthma [50]. In a retrospective study over a 1-year period, 19% of adult asthmatic patients admitted to a hospital were shown to have a concomitant respiratory infection [51].

Exercise is one of the most common inducers of asthma crisis. Exercise-induced asthma may be identified in the laboratory by exercise or isocapnic hyperventilation challenge [52]. Single preexercise treatment with inhaled β_2-agonists and/or sodium cromoglycate may prevent exercise-induced asthma [52].

The relationship between asthma and gastroesophageal reflux is well established but poorly understood [53]. Overnight intraesophageal pH study may confirm a suspected reflux [54]. Medical or surgical treatment of reflux can improve asthma [55, 56]. Theophyllines have been incriminated to worsen reflux by dilatating the lower esophageal sphincter, but a recent study reported no aggravation of nocturnal asthma in asthmatic patients with reflux treated by aminophylline [57]. Nonsteroidal anti-inflammatory drugs are the most common cause of drug-induced asthma [58]. The worldwide increasing automedication with nonsteroidal anti-inflammatory drugs may represent a potential danger for asthmatic patients that has not yet been evaluated by appropriate studies [8]. β-adrenergic blockers and antibiotics inducing hypersensitivity are also reported as precipitants of acute asthma attacks [59].

Food hypersensitivity is a less common triggering factor of asthma in adults than in children [59]. In contrast, alcoholic drinks are a frequent trigger of asthma [60]. Many patients with suspected food hypersensitivity have gastrointestinal and respiratory symptoms, but the diagnosis is often difficult to confirm, because there is a lack of highly reproducible tests [61]. Food challenges are difficult to interprete and may provoke anaphylactic reactions [62]. Food-induced asthma may be due to food itself, to the coloring, or to the added preservatives.

Stress, emotional conflicts, and other psychological factors must be considered as aggravating factors in some asthmatic patients [63].

The Treatment of ROAD

Assessing and staging the severity of the disease. The staging of ROAD should be based upon the severity of symptoms, the pattern and the importance of bronchial obstruction, and the amount of bronchodilators required to control the disease. Assessing the severity through the symptoms of the patients may be misleading, because perception of bronchial obstruction varies from patient to patient [64]. Therefore, the physician must look mainly for informations deriving from regular peak expiratory flow monitoring. Bronchial obstruction is a criterion of severity not only by its importance but also by its pattern. Daily measurement of peak expiratory flow rate may allow the classification of the pattern of bronchial obstruction: patients with stable asthma have a stable peak flow close to normal values; brittle asthma is characterized by highly variable peak flow values; deteriorating asthma is characterized by slowly diminishing peak flow values; patients with morning dips have low peak flow values only during the nighttime or the early morning [65]. The high variability of bronchial obstruction is a risk factor for exacerbation of the disease [66]. Current schemas of asthma staging have not been evaluated with appropriate clinical studies and are therefore, difficult to assess in terms of their applicability and their prognostic value. Asthma may be classified as mild, moderate, or severe. Patients with mild asthma have occasionally wheezing or tightness of the chest.

Their peak flow rate is mostly normal. They use occasionally inhaled bronchodilators, in periods with symptoms. Patients with mild asthma should be assessed regularly to confirm the mildness of their disease, because the frontier between mild and moderate asthma is far to be clear [67]. Patients with moderate asthma have daily symptoms and they use bronchodilators on daily basis. Their peak flow is under the limit of predicted value. Patients with severe asthma have prominent wheezing. They have disturbed sleep and morning chest tightness and they have often already been admitted to an hospital for severe exacerbation of their asthma [66]. They need administration more than 4 times a day of inhaled bronchodilators to control their symptoms. Their peak flow is less than 80% of predicted value.

Strategy of treatment. The objectives of treatment are to control symptoms, to allow the patient to pursue a normal life, and to control bronchial obstruction. To achieve these objectives, identified causative factors should be avoided. Although this is not always possible, allergen avoidance must be advised in patients where a specific allergen is identified. Immunotherapy may be discussed, though it has a restricted place in the treatment of asthma. Patients with mild asthma may be treated with inhaled β_2-agonist on demand. In patients with apparently mild asthma but also signs of bronchial inflammation, such as exacerbation of symptoms and bronchial obstruction, one should consider a prophylactic treatment with sodium cromoglycate or low doses of inhaled steroids. When permanent treatment is necessary, patients should not be treated only with bronchodilator drugs but also with anti-inflammatory and bronchodilator agents together. The stepwise plan must take into account the efficacy/side effects ratio of the drugs and the severity of the disease. Anti-inflammatory therapy for patients with mild asthma may begin with a trial of nedocromil or sodium cromoglycate for 3 months. If this trial fails, low doses of inhaled corticosteroids are indicated. The first-line bronchodilator treatment is an inhaled β_2-agonist. The narrow therapeutic index and the need of repeated measurements of theophylline blood level together, place theophylline in the second line of bronchodilator treatment [68]. Patients whose asthma cannot be controlled with the combination of an inhaled β_2-agonist and low doses of inhaled corticosteroids may benefit from the addition of a sustained-release theophylline preparation or anticholinergic drugs, in a therapeutic trial with a peak expiratory flow rate monitoring. Patients whose asthma cannot be adequately controlled with the previous association may benefit from increasing the inhaled dose of corticosteroids up to 2000 μg/day and, if needed, by a short course of oral corticosteroids until control is achieved. When symptoms and bronchial obstruction have been minimized, the treatment should be reduced to the minimum dose allowing to maintain the control of the disease. The optimal treatment is the treatment having the highest efficacy associated with the best tolerance. Regular follow-up and monitoring of peak flow rate are necessary to evaluate the efficacy and tolerance of the therapy and the education of the patients.

The nocturnal increase of asthmatic symptoms has been well documented in many asthmatic patients [69]. Poor pharmacologic control of airways during the nocturnal sleep may partly explain the high incidence of nocturnal asthma fatalities [67]. In these patients, the size of the morning dip may benefit from inhaled corticosteroids or inhaled β_2-agonists justifying a trial with these drugs [70]. However, this is not always the case and further treatment should be assessed, such as slow-release theophylline given once daily before bedtime [71].

Education of Patients with ROAD

Objectives of education. Many studies have emphasized the importance of patient participation in the management of ROAD [72]. Better education has been advocated to prevent severe asthma and death from asthma. The main goals of patient education are to obtain a degree of self-assessment and self-management by the patient. To obtain self-assessment, patients should be aware of the triggering factors of asthma and should be encouraged to avoid them. Self-assessment of the severity of the disease based upon symptoms often leads to underestimation and undertreatment [73]. The use of peak flow-meter permits to overcome of the problem of variable and often inaccurate subjective perception of airway obstruction in asthmatics [74] and enables the physician to assess the efficacy of the treatment. The patient's technique for using peak flow-meter should be checked repeatedly. The measurement of peak expiratory flow rate on daily basis is practical in order to assess bronchial obstruction, but it does not eliminate the need of regular spirometric measurements in the laboratory. Regular follow-up visits may help to supervise patients' self-management and allow the physician to assess the efficacy of the treatment. Teaching of self-management should enable patients to act appropriately in the event of an asthma crisis. They should learn which medication to use, how to practice subcutaneous injection of β_2-agonist, and when to call for medical aid. Educating programs aiming only to improve patients' knowledge of asthma were shown to be inefficient in reducing asthma morbidity in general practice [75]. Interpersonal reinforcement was shown to be more effective in reducing emergency department visits than written appeals in adult asthmatics [76]. A self-management plan based on routine assessment of peak flow was shown to substantially improve both subjective and objective assessment of asthma severity, to diminish symptoms, and to increase baseline lung function [77].

Technique of using inhalers and delivery systems. The rise in the mortality and the morbidity of asthma may be partly due to the undertreatment of the patients [78]. This includes both underestimation of severity by physicians and lack of optimal inhaled therapy. Effective inhalation can be obtained by teaching patients how to use the metered-dose inhaler. Education of patients with asthma takes time and should be regularly checked, because metered-dose inhalers are often misused [79].

The use of metered-dose inhalers needs a "hand-breath coordination" which is often difficult to obtain in certain patients such as children and elderly. The generally accepted proper maneuvers are: (1) shake inhaler, (2) place it 2 cm in front of the open lips, (3) exhale, (4) activate once, (5) inhale slowly and deeply, (6) hold breath for 10 s and breathe out slowly. The next puff is inhaled after a pause of about 1 min [80]. This pause has been shown to improve the bronchodilator efficacy of metered-dose inhalers [81]. The high speed of the inhaled cloud favors proximal deposition, bitter taste, and local side effects [82]. Additionally, numerous technique errors have been recorded [82]. These errors influence therapeutic efficiency, indicating the importance of supervising the inhalation technique both at the time of prescription and afterward [79].

Many patients find it difficult to use a metered-dose inhaler [83]. Hand-breath coordination problems can be overcome by using a spacer devices with the metered-dose inhaler or by the use of dry powder inhalers. The use of a spacer device is simple: The patient actuates the metered-dose inhaler that is attached to the chamber, then inhales the drug from the chamber. One single actuation of the metered-dose inhaler is recommended, to avoid the increased deposition of aerosol in the apparatus, resulting from successive actuations [84]. In patients with obstructive airways disease, the use of spacer devices has been shown to decrease the aerosol deposition in the oropharynx and to increase the deposition in the bronchi [84]. The bronchial response to a β_2 agonist is greater when using a metered-dose inhaler with a spacer device than when using a metered-dose inhaler alone [85]. A spacer device is as effective as a nebulizer in chronic stable asthma [84]. A high dose of inhaled corticosteroid treatment when administered via a spacer is associated with a reduced risk of oropharyngeal candidiasis and with an increased bronchial effect [29]. Patients with asthma requiring the use of spacer devices are those who are not able to use properly inhalers, who need more than 1500 μg beclomethasone per day or equivalent to control their disease, and patients in whom dose-limiting oropharyngeal side effects compromise the usefulness of inhaled corticosteroid therapy [29].

Hand-breath coordination problems may also be overcome by using powder inhalers. Powder inhalers have been shown to be as effective as metered-dose inhalers [87]. However, about 3% of patients with asthma have difficulties in using the powder inhaler properly [88]. The need to replace the capsule before each dosing diminishes the compliance of patients. Inhaler devices equipped with more than one dose of the drug are now available for both salbutamol and beclomethasone. The potential drawbacks of powder inhalers are coughing and proximal deposition. In conclusion, none of the current devices satisfies the needs of all patients and the method of delivery should be chosen for each individual patient.

Conclusion

The optimal long-term management of ROAD is based upon assessment of the diagnosis and the individual risk factors for exacerbation of the disease. The

treatment should be tailored to each individual patient by taking into account the efficacy/safety ratio of the medications. Education of the patient plays a major role in the successful long-term outcome of the treatment. This education should start with self-assessment by the patient, which consists of learning the potential risk factors and learning how to use properly and on a daily basis the peak flow-meter. Then patients should learn how to treat themselves following a stepwise management plan and should know when to call for medical aid.

Presently, most of therapeutic strategies are based upon clinical trials in which patients belong to an homogeneous population that is not representative of the whole population of asthmatic patients. Most published studies are designed to compare the potency of drugs to a placebo or to another drug. Any future improvement in the management of ROAD will be based upon trials that aim to reach a decision and to define a therapeutic strategy [89].

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April 7, 2008

VIA ELECTRONIC MAIL

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Re: Sepracor v. Barr

Dear Mr. Ratliff:

Thank you for your April 3, 2008 letter regarding the upcoming claim construction briefing. I had written precisely to confirm the scope of my understanding about our March 28 telephone conversation, so your clarifications are helpful to understand the issues.

With regard to the "second" point regarding the term "chronic," you state only that you do not agree that Sepracor's proposed construction of the term, i.e. "chronic" is inconsistent with Dr. Page's opinion. But Dr. Page defined the term differently, and his definition of the term is different than the plain and ordinary meaning of "chronic." Based on the March 28 telephone conversation, we may very well be in agreement on this issue, but I cannot tell. Please confirm how Sepracor believes that Dr. Page's interpretation of "chronic" is consistent with Sepracor's proposal.

With regard to the "first" and "fourth" points, my request here is simply to find out which claim terms will be the subject of claim construction. As you know, the opening round briefs on the issue are due on April 10, which is only three days away. There is no reason the parties should not know, at this late date, which claim terms are in dispute. Barr submitted its claim chart, and you and I discussed which claim terms are disputed. Subject to the resolution of the term "chronic," the other claim term at issue is "side effects." Sepracor provided no other term that it believes requires further construction. Of course, Barr reserves the right to participate in the resolution of whatever claim terms are actually briefed, even if Sepracor does not provide any advance notice.

Finally, regarding the "third" point, thank you for clarifying that you would check with local counsel about a proposed stipulation regarding agreed claim constructions. Per your request, I am sending a proposed stipulation along with this letter.

Very truly yours,

Imron T. Aly

cc: Richard K. Herrmann, Esq.
Jack B. Blumenfeld, Esq.
Elizabeth A. Leff, Esq.

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

SEPRACOR INC., Plaintiff, v. DEY, L.P., and DEY, INC. Defendants.	C.A. No. 06-113 (JJF) C.A. No. 06-604 (JJF) CONSOLIDATED
SEPRACOR INC., Plaintiff, v. BARR LABORATORIES, INC., Defendant.	C.A. No. 07-438 (JJF)

STIPULATED CLAIM CONSTRUCTION ORDER

The parties having stipulated and agreed to the following proposed claim constructions for asserted U.S. Patent Nos. 5,362,755; 5,547,994; 5,760,090; 5,884,002; and 6,083,993, the Court hereby ORDERS as follows:

1. For the purposes of this action, the term "optically pure R(-) isomer" in claim 1 of the '755 patent, claim 1 of the '994 patent, claim 1 of the '090 patent, and the term "optically pure R(-) albuterol" in claims 1, 4, and 10 of the '002 patent; and claims 1 and 10 of the '993 patent are construed to mean compositions "containing 90% by weight or more of the R(-) isomer."

2. For the purposes of this action, the term "substantially free of its S(+) isomer" in claim 1 of the '755 patent, claim 1 of the '994 patent, and claim 1 of the '090 patent are construed to mean compositions "containing 10% by weight or less of the S(+) isomer."

3. For purposes of this action, the term "an acute attack of asthma" in claim 1 of the '994 patent is construed to mean "an acute attack of asthma (a short and sharp course, not chronic)."

4. For purposes of this action, the term "suffering from an acute attack of asthma" in claim 1 of the '994 patent is construed to mean "experiencing an asthma attack, such as an episode of coughing, wheezing or gasping."

Farnan, J.

Exhibit 27

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VIA ELECTRONIC MAIL

April 30, 2008

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Re: *Sepracor v. Barr* – Claim Construction

Dear Mr. Ratliff:

This letter responds to your April 29 letter regarding claim construction briefing. Sepracor's view of the situation is completely backwards: Barr is not introducing any new argument; Barr is merely agreeing with Dey's proposed constructions when responding to the new arguments Sepracor raised in its opening claim construction brief. Given that Sepracor for the first time provided Barr with the constructions it now seeks for certain terms in its opening brief, Barr absolutely is entitled to respond in its responsive brief.

Sepracor created the situation that it now complains about. Your April 29 letter includes some of your correspondence regarding the claim construction issue, but fails to include the letters I sent to you on the same issue. In order to set the record straight, and to underscore Barr's repeated pleas to obtain Sepracor's proposed constructions for claim construction briefing, please see the attached correspondence. (March 26 Letter to Ratliff, March 31 Letter to Ratliff, and April 7 Letter to Ratliff).

The consistent theme in the correspondence is that Barr asked Sepracor repeatedly which terms were disputed and required any further construction, but that Sepracor ignored the requests. The parties discussed "side effects" at length, and Barr requested clarification about Sepracor's position on "chronic" to see if Sepracor really asserted that the term required no further construction (i.e., that it should simply mean "chronic"). Barr's efforts culminated in an April 7 letter to you, reiterating that "Sepracor provided no other term that it believes requires further construction." Your April 8 e-mail did not respond to the request for any terms that require further construction, and even for the "chronic" term, rather than say it should be

construed and should mean "recurring," you said that "Sepracor relies on the plain and ordinary meaning of the term." And while you claim that Sepracor informed Barr that certain terms would be disputed as between Sepracor and Dey, you did not provide any further proposed construction, perpetuating the impression that Sepracor did not seek to further construe claim terms other than "side effects."

Despite your compilation of all your correspondence, there is not one of them that shows Sepracor ever said that "chronic," "bronchospasm," and "reversible obstructive airway disease" require further construction and what those terms should mean. As an admission of this fact, your letter from yesterday actually directs Barr's attention to various other documents, such as portions of interrogatory responses for one term and briefing in the *Sepracor v. Breath* case for another. It is not enough to piece together these various sources now, because Sepracor had issued several inconsistent positions about these claim terms: correspondence in our case, interrogatory responses (which are different than the positions in Sepracor's brief), *Breath* case briefing (which does address the same terms), and expert reports (such as the Dr. Clive Page report, which offers yet another view). You should have provided a response to my April 7 letter that specifically asked you to identify which claim terms Sepracor proposed to be construed and how they should be construed. Instead, you ignored that request.

In any event, the claim terms that Barr seeks to address now that it is aware that Sepracor seeks to construe them – "chronic," "bronchospasm," and "reversible obstructive airway disease" – add no new terms to those already being addressed by Sepracor. In fact, the position taken by Barr with respect to these terms is merely to confirm its agreement with Dey and not with Sepracor as to the construction of the claim limitations that contain these terms. In the spirit of cooperation, Barr is willing to identify the intrinsic information upon which it will rely. Specifically:

Chronic should mean "prophylactic or periodic": Barr agrees with Dey's proposal because of the intrinsic evidence. The patent specification refers to administering "after onset" and "prophylactically," while the word "chronic" is not used. (*See, e.g.*, '755 patent, at col. 2, lines 28-36.) Indeed, Sepracor relied upon this same distinction during patent prosecution, and submitted the declaration of Dr. T. Scott Johnson dated May 11, 1994, which defines chronic as "prophylactic or periodic." And the PTO relied on this definition, as confirmed in the Notice of Allowability dated July 26, 1994.

Inducing bronchodilation or providing relief of bronchospasm should mean "treating asthma or an asthma attack": Barr agrees with Dey's proposal because of the intrinsic evidence. The patent specification consistently refers to the bronchial disorders of asthma and an asthma attack (*see, e.g.*, '755 patent, Abstract; col. 1, lines 22, 41-46 and 57; col. 2, lines 14-15, 29-36; col. 3, lines 20-24 and 25-27), but does not disclose any other conditions which might be treated with albuterol. Sepracor's prosecution history submissions dated February 10, 1993, July 23, 1993, and December 7, 1993, and the declaration of Dr. T. Scott Johnson dated May 11, 1994 also confirm the same conclusion, that the invention is directed exclusively to asthma or asthma attacks.

Reversible obstructive airway disease: Barr agrees with Dey's proposal because of the intrinsic evidence, for substantially the same reasons discussed above with respect to the bronchospasm claim limitation. In addition, Sepracor's prosecution history submission dated December 12, 1999 further confirms that this claim term refers to asthma or asthma attacks.

Finally, with respect to the stipulation, you still have not responded to my inquiry regarding the entry of the proposed order for claim term construction that actually appears to be agreed (optically pure, substantially free, acute asthma, and acute administration). I asked for your agreement in a letter dated March 31, then circulated a proposed order at your request on April 7, and reminded you that you did not respond to that letter in an e-mail on April 11. Even as of your letter from yesterday, you still did not state whether or not Sepracor agreed to enter an order regarding these stipulated terms. Therefore, we have no choice but to propose in our responsive pleading that those agreed terms should be entered in the form of an Order.

Regards,

Imron T. Aly

cc: Richard Herrmann
Elizabeth Leff

TAB A

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101 CALIFORNIA STREET SAN FRANCISCO, CA 94111 415-591-1000
100 NORTH TRYON STREET CHARLOTTE, NC 28202 704-350-7700
43 RUE DU RHONE 1204 GENEVA, SWITZERLAND 41-22-317-75-75
25 AVENUE MARCEAU 75116 PARIS, FRANCE 33-1-53-64-82-82
99 GRESHAM STREET LONDON, UNITED KINGDOM EC2V 7NG 44-020-7105-0000

VIA E-MAIL

March 26, 2008

Preston K. Ratliff II
Paul, Hastings,
Janofsky & Walker LLP
75 East 55th Street
New York, NY 10022

Re: Sepracor v. Barr

Dear Mr. Ratliff:

I am writing regarding the claim construction briefing in this case. As a preliminary matter, I again reiterate that Sepracor must produce all expert reports (with exhibits), interrogatory responses, and depositions (including video recordings) from the Breath and Dey cases to give Barr the opportunity to catch up with the accelerated schedule. That was the deal. Yet at this point, with two weeks left before *Markman* briefing, Sepracor still has not provided all of these requested materials, contrary to its agreement to produce them, and contrary to its representation to the Court that it would do so.

Surprisingly, I also learned today from the letters your colleague forwarded that the parties in the Dey case exchanged only claim terms to be construed, and not proposed constructions. I do not understand then the basis for your request that Barr should provide more information, when it has not been done in the Dey case pending for over a year longer. Still, per our agreement and in the spirit of cooperation, Barr submits the following proposed claim terms for briefing. Per our agreement, Sepracor is to provide tomorrow its proposal for claim terms, and the parties will then discuss tomorrow to see if any resolution can be reached.

Patent Claim	**Claim term**	**Proposed construction (based on the intrinsic evidence)**
'755: 1	side effects associated with chronic administration of racemic albuterol	If capable of being construed: Central nervous system effects (such as tremor, nervousness, shakiness, dizziness and increased appetite) and cardiac effects (such as cardiac

		arrhythmia) associated with chronic administration of racemic albuterol. See column 3, lines 28-31.
	comprising chronically administering	Comprising prophylactically administering
	a quantity of an optically pure R(-) isomer of albuterol sufficient to result in bronchodilation	A quantity containing 90% by weight or more of the R(-) isomer of albuterol sufficient to result in bronchodilation
	undesirable side effects	See above "side effects" term
	said R isomer being substantially free of its S(+) isomer.	Containing 10% by weight or less of the S(+) isomer of albuterol
'994:1	A method of treating an acute attack of asthma	A method of treating an acute attack of asthma (a short and sharp course, not chronic)
	side effects associated with the acute administration of racemic albuterol,	If capable of being construed: Central nervous system effects (such as tremor, nervousness, shakiness, dizziness and increased appetite) and cardiac effects (such as cardiac arrhythmia) associated with the acute administration (not chronic) of racemic albuterol. See column 3, lines 28-31.
	suffering from an acute attack of asthma	Experiencing an asthma attack, such as an episode of coughing, wheezing or gasping. See Aberg I, at ¶5.
	a quantity of an optically pure R(-) isomer of albuterol sufficient to result in bronchodilation	A quantity containing 90% by weight or more of the R(-) isomer of albuterol sufficient to result in bronchodilation
	undesirable side effects,	See above "side effects" term
	said R isomer being substantially free of its S(+) isomer.	Containing 10% by weight or less of the S(+) isomer of albuterol
'090:1	side effects associated with the administration	If capable of being construed:

	of racemic albuterol	Central nervous system effects (such as tremor, nervousness, shakiness, dizziness and increased appetite) and cardiac effects (such as cardiac arrhythmia) associated with the administration of racemic albuterol. See column 3, lines 28-31.
	a quantity of an optically pure R(-) isomer of albuterol sufficient to result in bronchodilation	A quantity containing 90% by weight or more of the R(-) isomer of albuterol sufficient to result in bronchodilation
	undesirable side effects	See above "side effects" term
	said R isomer being substantially free of its S(+) isomer.	Containing 10% by weight or less of the S(+) isomer of albuterol
'002:1	a quantity of optically pure R(-) albuterol sufficient to induce said bronchodilation.	A quantity containing 90% by weight or more of the R(-) isomer of albuterol sufficient to result in bronchodilation
'002:10	the concomitant liability of adverse effects associated with racemic albuterol,	If capable of being construed: Central nervous system effects (such as tremor, nervousness, shakiness, dizziness and increased appetite) and cardiac effects (such as cardiac arrhythmia) associated with chronic administration of racemic albuterol. See column 3, lines 28-31.
	a quantity of optically pure R(-) albuterol sufficient to induce said bronchodilation	A quantity containing 90% by weight or more of the R(-) isomer of albuterol sufficient to result in bronchodilation
	reducing said adverse effects.	See above "side effects" term
'993:1	optically pure R(-) albuterol.	Containing 90% by weight or more of the R(-) isomer of albuterol
'993:10	optically pure R(-) albuterol.	Containing 90% by weight or more of the R(-) isomer of albuterol

For all other claim terms, Barr proposes that they are to be given their plain and ordinary meaning, and objects to and disagrees with Sepracor's proposed constructions (which Sepracor represented are reflected in its response to Barr's Interrogatory No. 1).

Regards,

/s/
Imron T. Aly

TAB B

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IMRON T. ALY
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March 31, 2008

VIA ELECTRONIC MAIL

Preston K. Ratliff II
Paul, Hastings,
Janofsky & Walker LLP
75 East 55th Street
New York, NY 10022

Re: Sepracor v. Barr

Dear Mr. Ratliff:

This letter confirms our March 28, 2008 telephone conversation regarding claim terms that will be the subject of the upcoming claim construction briefing.

You reported that Sepracor's proposed claim constructions are not those found in its interrogatory responses, but instead those found in Sepracor's claim construction briefing submitted in the *Sepracor v. Breath* case. Barr is relying on that representation to understand Sepracor's proposals for the "side effects" claim limitation (or similar terms) found in the '755, '994, '090, and '002 patents. These claim limitations will be disputed in the upcoming briefing.

Regarding the claim term "chronic" in the '755 patent, you represented that Sepracor proposes that word to mean "chronic." This does not appear to be the same position advanced by Sepracor's expert, Dr. Page, in the *Breath* litigation. Would you please therefore confirm Sepracor's position, so that Barr can evaluate whether or not this is a disputed term?

The parties agree on the proposed construction for the following terms, and the parties will enter a formal stipulation and seek an Order to this effect:

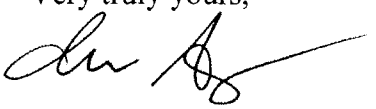
- "optically pure R(-) isomer" (and related terms) means "containing 90% by weight or more of the R(-) isomer"
- "substantially free of its S(+) isomer" (and related terms) means "containing 10% by weight or less of the S(+) isomer"

- "an acute attack of asthma" ('994 patent) means "an acute attack of asthma (a short and sharp course, not chronic)

- "suffering from an acute attack of asthma" ('994 patent) means "experiencing an asthma attack, such as an episode of coughing, wheezing or gasping"

Finally, you represented that Sepracor seeks no further construction for any other claim term in the asserted patents.

Very truly yours,



Imron T. Aly

TAB C

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April 7, 2008

VIA ELECTRONIC MAIL

Preston K. Ratliff II
Paul, Hastings,
Janofsky & Walker LLP
75 East 55th Street
New York, NY 10022

Re: Sepracor v. Barr

Dear Mr. Ratliff:

Thank you for your April 3, 2008 letter regarding the upcoming claim construction briefing. I had written precisely to confirm the scope of my understanding about our March 28 telephone conversation, so your clarifications are helpful to understand the issues.

With regard to the "second" point regarding the term "chronic," you state only that you do not agree that Sepracor's proposed construction of the term, i.e. "chronic" is inconsistent with Dr. Page's opinion. But Dr. Page defined the term differently, and his definition of the term is different than the plain and ordinary meaning of "chronic." Based on the March 28 telephone conversation, we may very well be in agreement on this issue, but I cannot tell. Please confirm how Sepracor believes that Dr. Page's interpretation of "chronic" is consistent with Sepracor's proposal.

With regard to the "first" and "fourth" points, my request here is simply to find out which claim terms will be the subject of claim construction. As you know, the opening round briefs on the issue are due on April 10, which is only three days away. There is no reason the parties should not know, at this late date, which claim terms are in dispute. Barr submitted its claim chart, and you and I discussed which claim terms are disputed. Subject to the resolution of the term "chronic," the other claim term at issue is "side effects." Sepracor provided no other term that it believes requires further construction. Of course, Barr reserves the right to participate in the resolution of whatever claim terms are actually briefed, even if Sepracor does not provide any advance notice.

Finally, regarding the "third" point, thank you for clarifying that you would check with local counsel about a proposed stipulation regarding agreed claim constructions. Per your request, I am sending a proposed stipulation along with this letter.

Very truly yours,

Imron T. Aly

cc: Richard K. Herrmann, Esq.
Jack B. Blumenfeld, Esq.
Elizabeth A. Leff, Esq.

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

SEPRACOR INC., Plaintiff, v. DEY, L.P., and DEY, INC. Defendants.	C.A. No. 06-113 (JJF) C.A. No. 06-604 (JJF) CONSOLIDATED
SEPRACOR INC., Plaintiff, v. BARR LABORATORIES, INC., Defendant.	C.A. No. 07-438 (JJF)

STIPULATED CLAIM CONSTRUCTION ORDER

The parties having stipulated and agreed to the following proposed claim constructions for asserted U.S. Patent Nos. 5,362,755; 5,547,994; 5,760,090; 5,884,002; and 6,083,993, the Court hereby ORDERS as follows:

1. For the purposes of this action, the term "optically pure R(-) isomer" in claim 1 of the '755 patent, claim 1 of the '994 patent, claim 1 of the '090 patent, and the term "optically pure R(-) albuterol" in claims 1, 4, and 10 of the '002 patent; and claims 1 and 10 of the '993 patent are construed to mean compositions "containing 90% by weight or more of the R(-) isomer."

2. For the purposes of this action, the term "substantially free of its S(+) isomer" in claim 1 of the '755 patent, claim 1 of the '994 patent, and claim 1 of the '090 patent are construed to mean compositions "containing 10% by weight or less of the S(+) isomer."

3. For purposes of this action, the term "an acute attack of asthma" in claim 1 of the '994 patent is construed to mean "an acute attack of asthma (a short and sharp course, not chronic)."

4. For purposes of this action, the term "suffering from an acute attack of asthma" in claim 1 of the '994 patent is construed to mean "experiencing an asthma attack, such as an episode of coughing, wheezing or gasping."

Farnan, J.